REMARKS

Claims 1-12, 14-16 and 24-26 are pending in this application. Claim 10 has been previously withdrawn from consideration. Claims 13 and 17-23 have been previously cancelled. In view of the Examiner's earlier restriction requirement, Applicants retain the right to present claim 10 in a divisional application.

35 USC § 102 Rejections

Claims 1, 7, 9 and 16 are rejected under 35 USC § 102(b) as being anticipated by WO 01/92288 ("Collins").

The Examiner asserted:

> WO Patent teaches contains a central vitamin core, which is an ophthamologically useful therapeutic compound. Therefore, all is necessary to arrive at the claimed subject matter is to select a compound having the bridged structure recited in claim 1. And, since adamantine and flumadine are named by the WO 01/92288 at the top of page 92, vitamin B conjugates of those compounds are anticipated by the prior art. (Instant Office action, Page 2).

Applicants respectfully traverse.

In order to anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc., v. Verisign, Inc.*, 2007-1565, October 20, 2008, (Fed. Cir. 2008). Finally, the law requires identity between the claimed invention and the prior art disclosure. *Kalman v. Kimberly-Clark Corp.*, 218 USPQ2d 781, 789 (Fed. Cir. 1983, *cert denied*, 465 U.S. 1026 (1984)).

Collins does not disclose ophthalmic compositions or diseases of the retina or posterior segment. The compounds shown on page 92 of Collins are examples of

antibiotics that contain an amine or an amide group. There is no indication from Collins that a topical ophthalmic composition is disclosed. Nor is there identical teaching of an efficacy enhancing component effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. Thus, each and every element of currently pending claims 1, 7, 9 and 16 is not taught by Collins.

In view of the foregoing, Applicants request withdrawal of the rejection of claims 1, 7, 9 and 16 under 35 USC § 102(b) as being anticipated by WO 01/92288 ("Collins")

35 USC § 103 Rejections

Claims 1-6, 7, 8, 9, 11-12, 14-16 and 24-26 are rejected under 35 USC § 103(a) as being unpatentable over Desantis, Jr. (US 2001/0047012) ("Desantis") and Collins et al. (WO 01/92288) ("Collins").

Applicants respectfully traverse.

A patent claim is in violation of 35 USC § 103(a) if the difference between the teachings of the prior art and of the claimed invention when taken as a whole are such that a person of ordinary skill in the art would find the claimed invention obvious in light of the prior art. *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (S. Ct. 1966).

The present invention is directed to a topical ophthalmic composition comprising a conjugated molecule comprising an efficacy enhancing component (EEC) and a therapeutic component (TC). Upon topical instillation of the ophthalmic composition, the EEC not only increases the partition coefficient of the TC, but is believed to bind the retinal epithelium, thereby selectively targeting the TC to the retina. See e.g., Specification, page 11, lines 3-28.

DeSantis et al. discuss various combinations of a) a glutamate antagonist and b) an IOP (intraocular pressure) controlling agent for the treatment of glaucoma or ocular hypertension. The list of glutamate antagonists include 6 very broad generic structures,

and all isomers and pharmaceutically acceptable salts thereof (these generic structures do not include amantidines), reference to additional compounds listed in a PCT application (WO 94/13275), and a list of 14 additional compounds. The number of glutamate antagonists listed in DeSantis et al., thus number in the thousands. One of the 14 additional compounds is memantine. See DeSantis et al., page 3, paragraph [0009] through [0018].

Likewise, DeSantis discloses that "the IOP-lowering agents useful in the present invention include all presently known IOP-lowering pharmaceuticals," including (without limitation) miotics, α and β adrenergic agonists, beta blockers, prostaglandins, carbonic anyhydrase inhibitors. See DeSantis et al., paragraph [0023]. Brimonidine is listed among such compounds.

DeSantis does not disclose and provides no reason for the person of ordinary skill to specifically select an admantidine-based glutamate antagonist for use as an efficiency-enhancing component or in a combination therapy from among the exceedingly large genus of possible combinations of "glutamate antagonists." See DeSantis at [0023].

But even more importantly, DeSantis does not disclose, and provides no reason for a person of ordinary skill in the art to make, a single, conjugated molecule comprising any one of the IOP-controlling compounds or glutamate antagonists disclosed therein.

Collins appears to be cited the Examiner simply to show that conjugated pharmaceutical agents are known. Collins does not disclose ophthalmic compositions or diseases of the retina or posterior segment.

In the United States Supreme Court case *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), Justice Kennedy affirmed that Graham v. John Deere continues to set forth the proper analytical test for obviousness. Pursuant to Graham, in an obviousness analysis, when "a person having ordinary skill in the prior art . . . would immediately see

that the thing to do was what" the inventor did, the invention is obvious. *Graham*, 383, U.S. at 24, 148 USPQ at 469 (emphasis added).

The KSR Court restated the Graham standard, stating that when there are "a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known opinions within his or her technical grasp." *KSR*, 127 S. Ct. 1727, 1742 (2007).

Even more recently, the United States Court of Appeals for the Federal Circuit clarified that "[t]he passage above in KSR posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinary skilled artisan of obviousness." *Ortho-McNeil Pharmaceutical, Inc v. Mylan Laboratories, Inc.* ___F.3d ___, ___USPQ2d___ (Fed. Cir. 2008) (emphasis added).

Chemical compositions were at issue in the *Ortho-McNeil* case. The court found that "the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route" that provided the claimed composition. In finding the claimed compounds non-obvious, the Ortho-McNeil court concluded that the prior art did not provide "the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Id.* at 9-10.

Applying the law of obviousness to the present case, it can be immediately seen that the combination of DeSantis and Collins does not provide any reason for a person of ordinary skill in the art to make ophthalmic compositions containing the conjugate of the present claims, comprising a therapeutic agent and an amantidine moiety targeting the posterior segment of the eye.

Both the United States Supreme Court, in *KSR*, and the United States Court of Appeals for the Federal Circuit in *Ortho-McNeil* have recently opined on the insidious nature of hindsight. In Ortho-McNeil, the court held that a person of ordinary skill in the art would have to have some reason to select the composition claimed from among

several unpredictable alternatives. The court held that this was extremely unlike since "the ordinary artisan in the field would have had to (at the time of the invention) without any clue as to the potential utility of [the compound] stop . . . and test it for properties" different from the purpose disclosed by the prior art. *Ortho-McNeil*, 2007-1223 at 9.

Here, the properties disclosed by DeSantis (anterior segment-acting IOP lowering activity) is far different than the posterior segment-acting neuroprotective activity of the present compositions. Nothing in the combination of DeSantis and Collins even remotely suggests testing a conjugate containing a therapeutic component and an EEC for retinal neuroprotective activity or delivery of a topical composition to the retina.

Thus, respectfully, the situation is here as it was in the Ortho-McNeil case, in which a fact-finder "simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention was obvious. Of course, this reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it 'would have been obvious at the time of the invention.'" *Id.* at 10 (emphasis added). Thus, "a flexible TSM [teaching, suggestion, motivation] test remains the primary guarantor against a non-statutory hindsight analysis" Id. at 11.

For this reason, the presently claimed invention is not prima facie obvious over DeSantis and Collins.

Even assuming *arguendo* that the present claims are *prima facie* obvious over the combination of DeSantis and Collins, secondary considerations conclusively rebut this presumption. While Applicants vehemently believe that the presently claimed invention is no*t prima facie* obvious over the combination of DeSantis and Collins, even if the Examiner were to find that a *prima facie* case of obviousness was established, these references teach away from the invention. Moreover, the activity of the claimed composition constitutes surprising results in light of the combination of DeSantis and Collins. Thus, there are strong secondary considerations that effectively rebut any

presumption that the presently claimed invention is obvious in light of DeSantis and Collins.

The combination of DeSantis and Collins actually teaches away from the present invention, since DeSantis is concerned with ocular hypertensive effects targeting the anterior segment of the eye and Collins does not disclose ocular therapeutics at all.

By contrast, as disclosed in the current specification, "the EECs of the present invention bind to the retinal epithelium. The binding of the EECs to the retinal epithelium may cause the TCs to become more bioavailable, in particular at or near the retinal epithelium." Specification, page 11, lines 8-12. The retinal epithelium is located in the posterior segment of the eye. Thus, the present conjugate serves to preferentially target the TC moiety of the topically applied conjugate to the posterior segment of the eye. Nothing in either DeSantis or Collins suggests or motivates one of ordinary skill in the art to make such compositions.

The present invention, which targets therapeutic agents to the posterior segment of the eye, represents a significant advance in the treatment of conditions of the posterior segment, since it is well known by those of skill in the art that ophthalmic agents tend not to migrate well to the posterior segment when topically applied to the ocular surface. As stated in the specification, many TCs may not have the proper lipophilicity to penetrate the various layers of the eye to reach the retina. Specification at page 10, lines 35-38.

In the December 26, 2005 Reply, the present Applicants provided data showing that the presently described prodrug conjugates are selectively targeted to melanin, which is preferentially found in the retinal epithelium located in the posterior segment of the eye, as described in the specification. These data have been resubmitted in the Declaration of Patrick M. Huges, Ph.D.

As outlined by Dr. Hughes in his Declaration, such selective retinal targeting would not be useful or desired in the methods and disclosure of DeSantis, since ocular

hypertension, with which DeSantis is largely concerned, is a condition of the anterior segment of the eye. It is therefore critical in the disclosure of DeSantis that the IOP-lowering agents remain in the anterior segment to lower IOP (for example by decreasing the rate of aqueous humor production in the ciliary body or by increasing the rate of uveal aqueous humor outflow) and thus help to prevent mechanical "crushing" injury to the retina.

The present claimed invention therefore functions in a completely different manner than the combination of glutamate receptor antagonists and IOP lowering agents cited by DeSantis. This difference in function would cause those familiar with DeSantis to discard the idea of making the conjugates of the present invention, since such conjugates would tend to migrate to the posterior segment, there by defeating the purpose of the combinations disclosed by DeSantis.

Collins discloses the use of conjugates comprising an antibiotic and a vitamin B12 or intrinsic factor-binding agent targeting moiety for targeting of antibiotics to infected tissue. However, the combination of Collins and DeSantis does not lead to the compounds and compositions of the present invention. If there were any reason at all to consider conjugating the IOP lowering agents and glutamate antagonist agents of DeSantis based upon the disclosure of conjugates provided by Collins, the person of skill in the art would immediately dismiss this idea as failing to provide a solution to the problem addressed by DeSantis; delivering an IOP lowering agent to the anterior segment of the eye.

For this reason, the combination of DeSantis and Collins teaches away from the present invention, which acts in a different and unexpected way. Even though Applicants do not believe that the prior art raises a *prima facie* case of obviousness, Applicants note that the United States Court of Appeals for the Federal Circuit indicates that "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect," In re Peterson,

315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003). Applicants submit that the present rejection is a clear example of this.

In addition, DeSantis' disclosure of the treatment of glaucoma through the administration of combination of an IOP lowering agent and a glutamate receptor antagonist in no way suggests the conjugates of the presently claimed ophthalmic compositions.

To be effective, DeSantis' combinations require that upon topical administration the glutamate receptor antagonists be present within the posterior segment of the eye, where they may interact with retinal ganglion cells and optic nerve fibers to prevent damage associated with excitotoxity. See DeSantis at [0007]. At the same time, in order to be effective in the manner disclosed by DeSantis the IOP lowering agent must be present in the anterior segment of the eye (such as the uvea and the ciliary body) to reduce ocular hypertension and thus help prevent retinal damage due to mechanical, circulatory, and other poorly understood factors associated with high IOP.

In other words, as disclosed by DeSantis, the IOP lowering agent and a glutamate receptor antagonist must act in different compartments (the anterior and posterior chambers, respectively) in order to function.

In the present invention, the TC and EEC are and must be targeted to the same intraocular locus (the posterior segment) by virtue of being linked in a single molecule.

Like the present invention, Collins also discloses molecular conjugates. However, the person of ordinary skill in the art would not look for a way to accomplish the effect of DeSantis by creating a single molecule comprising a TC and an EEC.

Only the present invention recognizes that the therapeutic components of the composite disclosed therein may be effective when the therapeutic agent is delivered to the posterior, rather than the anterior segment of the eye, and provides a composition effective to enhance such delivery.

For these reasons, the claimed invention is in condition for allowance.

The combination of DeSantis and Collins teach away from a conjugate-containing ophthalmic composition comprising an ophthalmically useful quinoxoline component and a covalently coupled admantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the arguments made herein with respect to claims 1-9, 11, 12 and 14-16 above. In addition, Applicants have the following comments.

The invention of claim 24 is directed to an ophthalmic composition comprising a conjugate that includes an ophthalmically useful quinoxaline covalently linked to an EEC of a given structure, wherein the conjugate is targeted to the posterior segment of the eye upon topical delivery of the composition. Claim 25 is directed to a subgenus of quinoxalines, while claim 26 is directed to the specific quinoxaline brimonidine tartrate.

Certain ophthalmically effective quinoxoline components are useful to lower intraocular pressure. For example, DeSantis discloses that the quinoxaline compound brimonidine is a useful alpha 2 agonist IOP lowering agent. DeSantis is generally drawn to the topical application of a combination of a glutamate receptor antagonist and an IOP lowering agent for the treatment of elevated intraocular pressure.

However, as outlined in the argument above with respect to claims 1-9, 11, 12, and 14-16, the problem and solution disclosed by DeSantis teach away from the use of IOP agents targeted to the posterior segment of the eye. The primary ocular hypotensive mechanism of action of quinoxalines, including brimonidine, is the activation of the alpha 2 adrenoceptors in the ciliary body, thereby decreasing cyclic adenosine monophosphate (cAMP) levels and thus decreasing aqueous humor production in the anterior chamber of the eye.

DeSantis' strategy of treating elevated IOP using a glutamate receptor antagonist and an IOP lowering agent depends upon efficient delivery of the IOP lowering agent to the anterior chamber of the eye. However, the present invention includes a conjugate compound that is specifically formulated to deliver the quinoxaline to the posterior chamber of the eye, where it may exert a neuroprotective activity. This activity is nowhere suggested in DeSantis or Collins, nor is the retinal epithelium targeting activity of the EEC of the present invention. This is indeed surprising result, as explained above.

Collins discloses conjugates, but does not render the present invention obvious in light of DeSantis, since, unlike the present invention, Collins is not concerned with preferentially delivering compounds to the posterior segment of the eye.

Thus, the combination of DeSantis and Collins does not lead one of skill in the art to the present invention but rather directs such a person away from a composition that delivers the quinoxaline, including brimonidine, to the posterior segment rather than the anterior segment of the eye. Because of this, the combination of DeSantis and Collins do not render the invention of claims 24-26 obvious.

The combination of DeSantis and Collins provide no reason, or suggestion why a person of skill in the art would make the present invention comprising an ophthalmic composition comprising an ophthalmically useful quinoxoline component and a covalently coupled admantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the argument made with respect to claims 1-9, 11, 12, and 14-16 above. In addition, Applicants have the following comments.

Specific IOP lowering quinoxaline compounds are alpha 2 receptor agonists that are believed to act on the alpha 2 adrenoreceptors located in the ciliary body of the eye to reduced aqueous humor outflow, thereby decreasing IOP. The ciliary body is located in the anterior chamber of the eye.

The combination of DeSantis and Collins provide absolutely no reason for the person of ordinary skill in the art to make ophthalmic compositions comprising the presently disclosed conjugates. The teachings of DeSantis would not lead, even in light of the disclosure of antibiotic/vitamin B12 conjugates disclosed by Collins, the person of ordinary skill in the art to opt to make a topical ophthalmic composition comprising a quinoxlaine- admantidine conjugate to target the posterior segment of the eye. This particularly true when the targeting of retinal epithelial tissue by the admantidine moiety of the conjugate appears to defeat the object of DeSantis to provide IOP lowering activity (which is provided in the anterior segment ciliary body for the alpha 2 agonist quinoxalines) in the combination therapy it discloses.

In view of the foregoing, Applicants respectfully request the Examiner to withdraw the rejection of claims 1-9, 11, 12, 14-16 and 24-26 under 35 USC § 103(a).

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 1 May 2009

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